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Clinical paper

Helium ventilation for treatment of post-cardiac arrest syndrome: A safety and feasibility study^{☆,☆☆,★}

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ABSTRACT

Aim: Besides supportive care, the only recommended treatment for comatose patients after cardiac arrest is target temperature management. Helium reduces ischaemic injury in animal models, and might ameliorate neurological injury in patients after cardiac arrest. As no studies exist on the use of helium in patients after cardiac arrest we investigated whether this is safe and feasible.

Methods: The study was an open-label single arm intervention study in a mixed-bed academic intensive care unit. We included 25 patients admitted after circulatory arrest, with a presenting rhythm of ventricular fibrillation or pulseless tachycardia, return of spontaneous circulation within 30 min and who were treated with hypothermia. Helium was administered in a 1:1 mix with oxygen for 3 h. A safety committee reviewed all ventilation problems, complications and causes of mortality.

Results: Helium ventilation was started $4:59 \pm 0:52$ (mean \pm SD) h after circulatory arrest. In one patient, helium ventilation was discontinued prematurely due to oxygenation problems. This was caused by pre-existing pulmonary oedema, and imposed limitations to PEEP and FiO_2 by the study protocol, rather than the use of helium ventilation. Sixteen (64%) patients had a favourable neurological outcome.

Conclusions: We found that helium ventilation is feasible and can be used safely in patients treated with hypothermia after cardiac arrest. No adverse events related to the use of helium occurred during the three hours of administration.

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Introduction

Out of hospital cardiac arrest (OHCA) is a major cause of morbidity and mortality, afflicting 335 per million per year in the Netherlands with an overall mortality of 81%.¹ Half of the patients admitted to the intensive care unit (ICU) leave the hospital with an

unfavourable outcome.^{2,3} Circulatory arrest and subsequent return of circulation leads to ischaemia reperfusion injury of the whole body and is particularly injurious to the brain and myocardium.^{4,5} Brain injury is the major cause of mortality and morbidity after cardiac arrest.⁶ Therefore, patients admitted after cardiac arrest should receive treatment aimed at reducing brain injury as part of the post-resuscitation care. The only effective treatment currently available is target temperature management.^{7–10} Despite this therapy, outcome results are disappointing and therapies to further reduce ischaemia reperfusion injury after OHCA are needed.

Helium reduces ischaemia reperfusion injury to the heart and the brain in animal models, suggesting that helium might be capable of reducing neurological and myocardial injury in patients after OHCA.^{11–17} However no clinical studies in this field have been done yet. Recently we demonstrated that helium induces preconditioning in healthy volunteers, thereby protecting against endothelial

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^{☆☆} This study was performed at the Academic Medical Center, University of Amsterdam, Netherlands.

[★] The study was registered with the Dutch Trial Registry (www.trialregister.nl), NTR2257, on 24 March 2010.

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dysfunction after regional forearm ischaemia.¹⁸ Clinically, helium is used to ventilate both adults and children with severe obstructive pulmonary disease and helium inhalation is generally considered to be safe.¹⁹ Prior to investigating the use of helium as a therapeutic agent in neurological damaged patients, we performed a safety and feasibility study, investigating whether helium ventilation can safely be used in patients admitted to the ICU after OHCA.

Methods

This was an open-label single arm intervention study, performed in the mixed surgical and medical ICU of the Academic Medical Centre, Amsterdam, the Netherlands. The study was approved by the medical ethics committee of the Academic Medical Centre (protocol number NL 30466.018.09) and was conducted in concordance with the principles of the declaration of Helsinki and good clinical practice. Patients were included after obtaining informed consent from their legal representative.

Inclusion criteria were admission after witnessed OHCA, with the first registered rhythm being ventricular fibrillation (VF) or tachycardia (VT) and treatment with mild hypothermia (target temperature 33 °C). Return of spontaneous circulation (ROSC) had to occur within 30 min and helium ventilation had to be started within 6 h after cardiac arrest. Exclusion criteria were oxygenation problems (necessitating a $\text{FiO}_2 > 50\%$ and $> 10 \text{ cmH}_2\text{O}$ positive end expiratory pressure [PEEP]), neurological deficits or severe disability before cardiac arrest, comorbidities with a life expectancy of less than 6 months and pregnancy. The described ventilation settings were limits during the study-protocol as well.

Study procedures

After inclusion, helium ventilation was initiated as soon as possible. Helium was administered using a heliox compatible Servo-I ventilator (Maquet, Netherlands), which was calibrated to accurately measure tidal volumes when using heliox. Helium was supplied from a pressurised cylinder containing 1780 L heliox (Heliox21, BOC Ltd., UK), as a 79/21 helium/oxygen mixture, and was mixed in the ventilator with oxygen to obtain a final gas mix of 50% helium and 50% oxygen. Helium ventilation was done in pressure control mode, which was the standard ventilation mode in our ICU, peak pressure was set to achieve a tidal volume of 6 ml/kg ideal body weight, with 5–10 cmH_2O of PEEP and the respiratory frequency was controlled to maintain a pCO_2 of 4.5–5.5 kPa and a pH of 7.35–7.45 (alpha-stat). A pO_2 of $\geq 10 \text{ kPa}$ and a saturation of $\geq 95\%$ were aimed for. After switching to helium, a setup period with repeated blood gas analyses was used to reach the target values for pCO_2 and pH. When these measurements were within the target values helium ventilation was continued for a 3-h period. Since the objective of this study was to investigate the safety and feasibility, and not the effectiveness, helium ventilation was stopped if the cylinder was empty before the end of the 3-h period.

Data collected were age, gender, Body Mass Index (BMI), simplified acute physiology score II (SAPS II), acute physiology and chronic health evaluation score II (APACHE II), pre-existent cardiovascular disease or malignancy, cause of arrest, time until first shock, time to ROSC, the use of coronary angiography and percutaneous coronary interventions and the need for haemodynamic support at admission.

Serum samples for analysis of creatine kinase (CK), creatine kinase muscle-brain (CK-MB) and troponin-T were drawn at admission and at 6, 12, 18, 24, and 48 h. Serum samples for analysis of neuro specific enolase (NSE) levels were drawn 24 and 48 h after admission. NSE serum samples were centrifuged and stored at -80°C until analysis by immunoassay (kit for ELECSYS, Roche).

Table 1
Baseline characteristics.

	Patients (25)
Male sex	20 (80%)
Age (years)	64.8 ± 12.1
BMI ^a (kg/m^2)	27.4 ± 4.8
SAPS II score ^b	53.6 ± 18.6
APACHE II score ^c	20.0 ± 8.6
Comorbidity cardiovascular disease	14 (56%)
Malignancy	4 (16%)
Cause of OHCA ^d Acute infarction	17 (68%)
Chronic infarction	4 (16%)
Structural heart disease	3 (12%)
Unknown	1 (4%)
Time to 1st shock (min)	8 ± 7
Time to ROSC ^e (min)	16 ± 7
CAG ^f ,	20 (80%)
PCI ^g	15 (60%)
IABP ^h or impella	9 (36%)
Inotropics or vasopressors	12 (48%)

^a Body Mass Index.

^b Simplified acute physiology score II.

^c Acute physiology and chronic health evaluation II.

^d Out-of-hospital cardiac arrest.

^e Return of spontaneous circulation.

^f Coronary angiography.

^g Percutaneous coronary intervention.

^h Intra-aortic balloon pump.

Outcome was assessed by telephone interview of the patient or caregiver 30 days after admission. The Glasgow Outcome Scale (GOS) was used; poor outcome was defined as death or vegetative state (GOS 1–2).²⁰ Primary objective of the study was to investigate the safety and feasibility of helium administration in patients after cardiac arrest. Safety endpoints were the inability to adequately ventilate the patient using helium within the predetermined limits ($\text{FiO}_2 50\%$ and $\leq 10 \text{ cmH}_2\text{O}$ PEEP), and death related to helium. To determine the probability of an adverse event being related to helium treatment all serious adverse events were evaluated by an independent safety committee, consisting of an independent intensive care physician, anaesthesiologist and neurologist.

Secondary objectives were to investigate the effect of helium ventilation on outcome (GOS), brain injury (NSE) and cardiac injury (CK, CK-MB, and troponin-T).

Statistics

There is no data on the effectiveness or the occurrence of adverse events of helium treatment in patients after OHCA. Therefore, a formal sample size calculation could not be performed. We expected a mortality rate of approximately 50%, and therefore chose to include 25 patients, to be able to detect an increase in adverse events related to helium. This is also a sample size that is used in similar studies.^{21,22}

SPSS 19 (IBM, Armonk, New York, USA) was used for statistical analysis unless stated otherwise. Continuous data are presented as mean with standard deviation when normally distributed, and otherwise as median and interquartile range, while categorical data are presented as numbers with proportions.

Results

Between April 2010 and October 2011, 106 patients admitted after OHCA were screened for eligibility, of which 64 patients were not eligible, 13 patients were eligible but were missed by the physician on call, in four patients study participation was refused by the

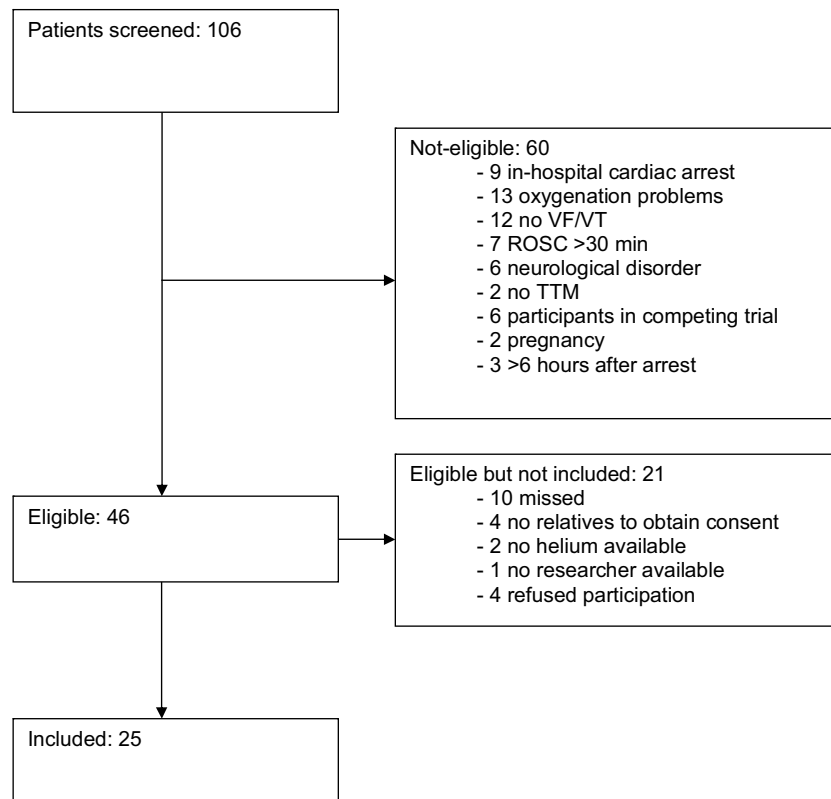


Fig. 1. Flow schedule of patients.

legal representative, and finally 25 patients were included (Fig. 1). Baseline characteristics of patients are presented in Table 1.

Helium ventilation was started $4:59 \pm 0:52$ (mean \pm SD) h after arrest, and 21 ± 13 (mean \pm SD) min was used to reach stable ventilator settings with $p\text{CO}_2$ and pH within target range. After that, helium ventilation was continued for a total of $3:10 \pm 0:39$ (mean \pm SD) h. One patient was ventilated longer than the planned 3-h period. The effect of helium ventilation on blood gas values and respiratory settings is described in detail elsewhere.²³ In six patients the treatment was stopped prematurely; in five patients the heliox cylinder was empty before completion of the 3-h treatment protocol, due to high minute volumes needed and the duration of the adjustment period. In one patient, ventilation with helium was terminated prematurely. This patient had slight hypoxia at the time of inclusion due to pulmonary oedema following cardiac arrest, requiring 10 cmH₂O PEEP and a FiO_2 of 50% to maintain an oxygen saturation (sO_2) of $>90\%$ and a PaO_2 of 8.4 kPa. Shortly after the initiation of helium ventilation, the sO_2 dropped to 84% and the PaO_2 to 7.1 kPa, thereby meeting a safety endpoint, and it was decided to discontinue the study protocol and switch back to a normal gas mixture. Only after increasing FiO_2 to 70% and PEEP to 12, oxygenation improved in this patient. These ventilation settings had to be maintained for several days. As the hypoxia was pre-existing and persisting, the safety committee concluded that the ventilation disorders were not caused by the short use of helium. Although helium treatment was stopped for safety reasons, this was probably due to the restrictions the study protocol posed on the settings of PEEP and FiO_2 , rather than the use of helium itself.

Nine patients died within 30 days (36%); in all patients post-anoxic brain injury was the cause of death. None of these deaths were related to helium ventilation. At 30 days follow-up, the surviving 16 patients (64%) all had a favourable outcome, 13 patients

(81%) resided at home, two patients (13%) in a rehabilitation centre and one patient was still hospitalized (6%).

Helium treated patients had a mean NSE value of $44 \pm 51 \mu\text{g l}^{-1}$ at 24 h, and $54 \pm 94 \mu\text{g l}^{-1}$ at 48 h after arrest.

Discussion

This is the first study focusing on the use of helium as a treatment for post cardiac arrest syndrome. We found that helium ventilation is feasible and can be used safely in patients treated with hypothermia after OHCA. No adverse events related to the helium ventilation occurred during the three hours of ventilation with this noble gas.

These results might open the door to a new treatment of brain injury following cardiac arrest. Helium might reduce the reperfusion injury, but our study was not designed to demonstrate this and subsequent studies on the potential therapeutic value of helium in organ protection following ischaemia reperfusion are needed. Although the mortality rate is lower than values normally reported in the literature for ICU patients admitted after cardiac arrest, this is probably due to the patient selection.^{3,24} We included only patients who had a witnessed arrest, presented with VF or VT, and had a resuscitation time of thirty minutes or less, all factors that have a positive effect on outcome.

Comparison of our results to studies with helium or other noble gasses in patients after cardiac arrest is not possible, as this has never before been studied. Only animal studies have been performed showing conflicting results regarding neuroprotective properties of helium. In an *in vitro* model of traumatic brain injury, Coburn et al. found a protective effect of helium, and Pan et al. found a reduction in infarct size by helium inhalation in an *in vivo* rat model using MCA occlusion.^{12,13} More positive effects in a MCA occlusion model were reported by David et al. but this protective

effect was only seen when the animals were allowed to cool down in a flow chamber.¹⁶ The authors suggested that the protection was mediated by the induction of hypothermia. Finally, in neonatal rats in which one common carotid artery was temporally occluded, Liu et al. demonstrated neuroprotection by helium, and Zhuang et al. confirmed this protection for ischaemia of 90 min, but not for 120 min.^{17,25} Other studies did not find a beneficial effect of helium on cerebral injury. In an *in vitro* model using oxygen glucose deprivation to induce brain injury, Jawad et al. did not find any beneficial effect.²⁶ Pan et al. used a model of MCA occlusion and reported that helium only provided protection when given directly at the time of reperfusion, and in an inspired fraction of 70%.²⁷ Until today, the exact underlying mechanisms mediating possible organ protective effects of helium are unclear.²⁸

Other noble gasses are also being investigated as neuroprotective agents. In a pig model of cardiac arrest, xenon was given after resuscitation and reduced brain injury.²⁹ The use of xenon in patients after cardiac arrest seems feasible and safe, although a specially designed ventilator is required.³⁰ A subsequent randomised controlled trial of 110 patients was published very recently and found a reduction in white matter injury on MRI, but no improvement in survival or neurological outcome.³¹ Xenon is also under investigation as a treatment for neonatal encephalopathy, but a first randomized controlled trial found no benefit on neurological injury in these patients.³² Helium is less scarce than xenon and cheaper, and while xenon requires purposely-designed ventilators, helium can be administered using common ICU ventilators. If helium ventilation is an effective neuroprotective strategy in patients after OHCA, the application in daily clinical care in the ICU will be much easier than xenon ventilation.

It is known that the results of animal studies investigating neuroprotection in different animal models are difficult to translate to the human situation. Many neuroprotective drugs have been studied in stroke patients, based on positive animal experiments, but no effective drug has ever been found for humans.^{33,34} A large difference with focal ischaemic stroke models is that in patients after OHCA the vasculature of the brain is intact and open. As soon as circulation is restored, neuroprotective agents can easily reach the brain cells and perform their actions.

We chose to start with a small study, which makes conclusions about possible effectiveness insignificant and might underestimate the side effects of helium ventilation. Especially longer periods of helium ventilation, which might be needed for an optimal treatment effect, could lead to more problems. This would be the logical topic to address in a subsequent study.

Second, the open-label use of helium inadvertently introduces a risk for bias, however by using endpoints that are not influenced by observer interpretation (mortality, vegetative state and laboratory assessments) the risk for observer bias was reduced.

Third, the setting of a single ICU of a university hospital limits extrapolation of the results. However, since the objective of the study was to investigate the safety and feasibility, we feel that these limitations are of minor concern at this stage.

All patients were ventilated with 50% helium in order to give the same dosage. This also meant that all patients received 50% oxygen, regardless of their oxygenation status, which could lead to supnormal oxygen tensions in some patients. A high PaO₂ during or after cardiac arrest has been linked to an increase in mortality, and might influence a beneficial effect of helium.^{35–37}

Prior to further clinical trials, subsequent research should include a relevant animal study, such as a porcine model of cardiac arrest, to strengthen the data on the efficacy of helium, and to answer questions on the required inspiration fraction, the optimal duration of treatment and the effect of delay between arrest and the start of helium treatment.

Conclusions

We demonstrated for the first time that helium ventilation for three hours is safe and feasible in patients after OHCA. This might open the route for further studies investigating the effectiveness of this new organ protective treatment modality.

Conflict of interest statement

The authors declare they have no competing interests.

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Authors' contributions

DB, NJ, BP and JH designed the study, DB, CB, WvdB, WL, NJ and JH included the patients, executed the study-protocol and collected the data. DB, JB and JH analysed the data, and DB and JH wrote the first draft of the manuscript, all authors contributed to the final version.

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